Université de Montréal

Évaluation de l'impact de la maladie de Kawasaki sur le développement neurocognitif

Par

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Résumé

Introduction : La maladie de Kawasaki (MK) est une vascularite immunitaire transitoire se manifestant majoritairement chez les enfants d'âge préscolaire. Différentes atteintes neurologiques ont été répertoriées en phase aigüe, la plus fréquente étant une irritabilité excessive associée à une inflammation du système nerveux central. Les conséquences potentielles de la MK sur le développement cognitif, comportemental et cérébral des enfants demeurent peu étudiées.

Objectifs : Cette étude pilote vise à (1) décrire le profil neuropsychologique d'enfants d'âge scolaire primaire ayant eu la MK et (2) explorer les impacts sur des marqueurs électroencéphalographiques (EEG) associés à l'attention et à la maturation cérébrale.

Méthode : Quinze enfants (âgés de 8.8±2.5 ans) ont été recrutés pour l'étude, en moyenne 4.9±2.7 ans après avoir eu la MK. Une évaluation des fonctions intellectuelles (Wechsler Intelligence Scale for Children – 5th Edition), de l'attention soutenue auditive (Test of Everyday Attention for Children) et de la mémoire épisodique verbale (California Verbal Learning Test for Children) a été effectuée. Les parents ont répondu à 4 questionnaires standardisés pour évaluer 1) le fonctionnement exécutif (Behavior Rating Inventory of Executive Function); 2) les problèmes internalisés et externalisés (Child Behavior Checklist); 3) les symptômes du Trouble déficitaire de l'attention avec hyperactivité (Conners-3) et 4) les symptômes du Trouble du spectre de l'autisme (Social Responsiveness Scale-2). La fréquence de participants présentant une performance cognitive plus faible (≤ 1 écart-type sous la moyenne normative) et/ou des difficultés comportementales potentielles (≥ 1 écart-type au-dessus de la moyenne normative) a été calculée. Le ratio thêta/bêta et le pic alpha ont été extraits du signal EEG de repos et comparés aux données de 32 enfants contrôles (8.9±2.1 ans). Un algorithme de réduction de dimensions a été utilisé sur la bande alpha pour détecter des tendances inter et intra-groupes.

Résultats : Les fonctions intellectuelles et mnésiques des participants se sont avérées dans les normes. Toutefois, une proportion importante d'enfants a performé dans la moyenne faible ou dans la zone limite à la tâche attentionnelle (4/14; 29%). Les réponses parentales ont révélé des proportions considérables d'inattention (6/14; 43%), de difficultés en mémoire de travail (7/14; 50%) et d'hyperactivité-impulsivité (5/14; 36%). Alors qu'aucune différence au niveau du ratio thêta/bêta n'a été soulevée, le ratio d'amplitude du pic alpha du groupe clinique s'est avéré

significativement plus faible que celui du groupe contrôle, montrant un pic atténué dans 4 des 6 régions étudiées ($p<0.05$ au Mann-Whitney). L'algorithme de réduction des paramètres de la bande alpha a révélé une séparation franche des participants MK en deux sous-groupes. Le sous-groupe ayant une bande alpha davantage atténuée comportait plus d'enfants ayant présenté de l'irritabilité en phase aigüe (8 vs 1; test exact de Fisher $p = 0.023$).

Conclusions : Malgré des aptitudes cognitives globalement préservées, nos résultats suggèrent une association potentielle entre la MK et des difficultés attentionnelles ultérieures. Cette première étude en EEG fournit une indication préliminaire d'un pic alpha atténué après la MK, plus particulièrement chez les patients ayant présenté une irritabilité marquée en phase inflammatoire. Des études à plus grande échelle sont nécessaires afin de confirmer les présents résultats et de mieux caractériser la trajectoire développementale des patients.

Mots clés : maladie de Kawasaki, enfants, neuropsychologie clinique, attention, électroencéphalographie, oscillations cérébrales, pic alpha

Abstract

Objectives: Acute Kawasaki disease (KD) induces excessive irritability and central nervous system inflammation. Long-term impacts of KD on children's cerebral and cognitive development have only been marginally studied. This pilot study aims to (1) describe the neuropsychological profile of primary-school-aged children with a history of KD and (2) explore the impacts of the disease on electroencephalographic (EEG) markers associated with attention and brain maturation.

Study design: Fifteen children aged 8.8±2.5 years participated in this project 4.9±2.7 years after KD onset. Intellectual abilities, long-term verbal memory, and auditory sustained attention were evaluated. Parents completed four standardized questionnaires to assess 1) executive functioning; 2) internalizing and externalizing difficulties; 3) Attention Deficit Hyperactivity Disorder symptoms; and 4) Autism Spectrum Disorder symptoms. Frequencies of participants presenting lower cognitive performance (≤ 1 standard deviation below normative average) and/or potential behavioral difficulties (≥ 1 standard deviation above norms) were calculated. Theta/beta ratio (TBR) and alpha peak (AP) were extracted from resting-state EEG and compared to 32 matched controls (8.9±2.1 years). Alpha band was analyzed using a feature reduction algorithm to detect potential groupings.

Results: Performances showed preserved intellectual abilities and memory. Sustained attention was in the limit or low average for 4/14 children (29%), with considerable parental reports of inattention (43%), working memory difficulties (50%), and hyperactivity symptoms (36%). While no alterations in TBR were found, a significantly lower AP amplitude ratio was revealed in KD compared to controls. A clear separation of the KD cohort into two clusters showed that acute irritability is associated with a globally weaker AP ($p = 0.023$).

Conclusions: Despite overall preserved cognitive functions in primary school-aged children, there is a possible association between KD and attention deficit concerns. This first EEG-based study indicates alpha peak abnormality after KD, predominantly in children with acute irritability. Longitudinal studies are warranted to better characterize patients' developmental trajectory.

Key words: Kawasaki disease, children, clinical neuropsychology, attention, electroencephalography, brain oscillations, alpha peak

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(**Top**) Mean alpha peak amplitude ratio (APAR) for the Kawasaki disease group (KD – dashed bars) and control group (CO – plain) in the six regions of interest (left frontal (F3), right frontal (F4), frontocentral (FCz), central (Cz), parietal (Pz), and occipital (Oz)). Errors bars are standard deviations. The APAR is significantly lower in KD in FCz, Cz, Pz, and Oz regions (Mann-Whitney U test. $*p < .05$ $**p < .01$). (**Bottom**) Schematic representation of the 6 regions of interest in a 10-20 system of electrode placement (adapted from Electrical Geodesics System Inc.).

(**A**) The two-dimensional projection of the 24-dimensional alpha curve profile metrics for KD and CO subjects shows poor separation between groups, while (**B**) KD patient subgroup clustering shows two well separated embeddings as shown in (**C**) where a KD2 subgroup had a higher number of patients with acute irritability as opposed to a KD1 subgroup.

Liste des sigles et des abréviations

ADHD: Attention Deficit Hyperactivity Disorder

AP: Alpha peak

- APA: Alpha peak amplitude
- APAR: Alpha peak amplitude ratio
- APF: Alpha peak frequency

ASD: Autism Spectrum Disorder

BRIEF: Behavior Rating Inventory of Executive Function

CBCL: Child Behavior Checklist

CNS: Central nervous system

CVLT-C: California Verbal Learning Test for Children

EEG: Electroencephalography

FSIQ: Full-scale intellectual quotient

IL-6: Interleukin-6

KD: Kawasaki disease

PSD: Power spectral density

SRS-2: Social Responsiveness Scale – 2nd Edition

TBR: Theta/beta ratio

TEA-Ch: Test of Everyday Attention for Children

t-SNE: t-distributed Stochastic Neighbor Embedding

WISC-V: Wechsler Intelligence Scale for Children – 5th Edition

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Avant-propos

L'article découlant de cette étude pilote est présenté dans les prochaines pages du document. Il a été soumis en tant qu'article original à la revue *The Journal of Pediatrics* en fin avril 2022. Au moment de rédiger ces lignes, nous sommes en attente d'une première décision de la part des éditeurs.

Article

Long-term impacts of Kawasaki disease on child development: a pilot study on cognition, behavior, and electroencephalography markers

SHORT TITLE: Long-term impacts of Kawasaki disease on child development

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DATA AVAILABILITY STATEMENT: The original contributions presented in the study are included in the article and Supplementary material, further inquiries can be directed to the corresponding author.

1. Introduction

Kawasaki disease (KD) is an acute multisystemic vasculitis of unknown etiology that manifests mainly in children under 5 years of age[1]. Although treatment with intravenous immunoglobulin greatly reduces the incidence of coronary artery aneurysms, KD is still the leading cause of acquired heart disease in children of developed countries[2]. Its diagnosis is based on the sequential onset of multiple and heterogenous symptoms[3].

Most studies have focused on cardiac and immunological implications of the disease, with sparse interest in central nervous system (CNS) involvement. However, neurological complications in KD have been described since the 1980s and are seemingly observed in 1 to 30% of patients[4, 5]. In a recent retrospective study, almost 50% of patients with neurological symptoms had shown CNS impairment as the initial and/or predominant manifestation of KD[6]. Acute CNS involvement can present in various clinical forms, thus complicating diagnosis and treatment.

One of the most common neurological manifestations in KD is an extreme irritability at presentation[3]. This excessive irritability would be caused by cerebral inflammation, as reflected by elevated cerebrospinal fluid inflammatory factors such as interleukin-6 (IL-6) and tumor factor necrosis alpha[7-10]. Cerebrospinal fluid levels of IL-6 in KD can be similar to those found in aseptic meningitis[8], a condition that has been diagnosed in almost 40% of KD patients who underwent lumbar puncture[10].

While excessive irritability manifested by patients resolves with response to treatment, studies have shown behavioral sequelae lasting from months to years after KD. Using standardized parental ratings, internalized difficulties (e.g., somatic complaints, anxiety, social problems, and withdrawal[11-13]) were found in up to 40% of children with past KD[12]. External difficulties including hyperactivity, aggressivity, and conduct problems have also been reported. [12, 14, 15] Intellectual impairment has been discarded by previous studies[11, 16-19], but attentional concerns have been documented[11, 15], raising questions about a potential association between KD and Attention deficit hyperactivity disorder (ADHD). To date, studies investigating this issue have yielded inconsistent results[19-21]. However, no studies have objectively evaluated (with neuropsychological testing) attentional capacities of these children.

Other complications such as cranial nerve involvement leading to sensorineural auditory loss, ataxia or transient facial palsy have also been reported[15, 22]. It is to note that CNS involvement can occur even in patients without explicit neurological symptoms. As such, single-photon emission computed tomography studies have revealed asymptomatic focal cerebral hypoperfusion in 29 to 72% of patients[23, 24]. This hypoperfusion lasted for almost two years in some children, suggesting that the usually minor impact of KD on brain blood flow could eventually accumulate[24].

Overall, the considerable evidence of cerebral implication in KD compels us to investigate if this association can affect subsequent brain development and/or lead to neuropsychological impairment. The long-term consequences of KD on brain function have never been properly addressed, most studies being limited to within two years from acquiring the disease. We therefore conducted a comprehensive neuropsychological evaluation with cognitive and behavioral assessment in association with non-invasive electroencephalography (EEG) exploring the brain electrophysiological dynamics 5 years after KD. Considering the possible association between KD and ADHD, the analysis of EEG power spectrum metrics that are known to be related to attentional capacities is relevant. As such, one of the most consistent findings in ADHD is a higher power in the low-frequency theta range (4-8 Hz) combined with a reduced power in high-frequency beta range (13-30 Hz) [25-28]. This power difference, usually described in a resting condition, is referred to as the theta/beta ratio (TBR). The use of the TBR as part of the ADHD diagnosis has been approved by the US Food and Drug Administration in 2013[29]. Correlations between elevated frontal TBR and lower attentional control and inhibition have also been found in healthy individuals[30].

Another largely studied marker in EEG oscillatory power spectrum is the alpha peak (AP), a peak usually found between 7 and 13 Hz that is stronger at posterior and occipital regions[31]. The AP frequency (APF) corresponds to the discrete frequency in the alpha band with the highest amplitude. This marker is strongly related to chronological age, with a mature alpha peak of 10 Hz usually reached at the age of 10 years old [32-34]. The increase of APF with age would reflect global developmental changes in gray and white matter, as well as in cortico-thalamic networks [34]. This marker would also reflect general cognitive functioning[35-41]. Consistently, children and adolescents with learning disorders, autism, and ADHD show phenotypes with lower APF [32, 42, 43]. The APF has been described as a marker of global architectural and functional properties of the human brain

as well as being a promising neurophysiological trait marker for investigating the association between brain and cognitive functioning [40].

1.1. Objectives and hypotheses

The first main objective of this pilot study was to characterize children's neuropsychological profile years after KD in terms of the following domains: intellectual abilities, long-term verbal memory, auditory sustained attention, executive functioning at home, internalized/externalized difficulties, ADHD symptoms, and Autism Spectrum Disorder (ASD) related social behavior. Given the exploratory and descriptive nature of this objective, no specific hypotheses were made.

The second main objective of our study was to explore long-term integrity of electrophysiological brain markers after KD in a search of an abnormal index of attention (i.e., theta/beta ratio) and of maturation (i.e., alpha peak). This study is the first to investigate these biomarkers in a KD population, and therefore the objective remains exploratory.

2. Methods

2.1. Participants

To be eligible, participants had to: 1) have been diagnosed with KD in accordance with the American Heart Association criteria[3] at least 6 months before testing; 2) be 6 to 12 years old at assessment; 3) speak French as their first language; 4) have attended elementary school for at least 6 months, and 5) have no psychiatric history or neurological conditions unless secondary to KD if applicable. Twenty-eight patients were screened eligible for the project based on their medical file: 17 families were approached, 2 recused themselves for lack of time and 15 consented to participate. The study protocol was reviewed and approved by the ethics, administrative, and scientific committees at the Sainte-Justine's Research Center. All subjects and their parents gave informed verbal and written consent to participate, following a full explanation of the procedures.

In order to compare EEG findings, a control group (CO group) was composed of 32 healthy children that had previously participated in research projects conducted in Dr Sarah Lippé's laboratory in Sainte-Justine's Research Center. They were matched with KD group by sex, age

(± 1 year), and Wechsler's FSIQ (± 10 points). These participants had been recruited via social media, posters in Sainte-Justine's hospital and advertisements in Montreal elementary schools.

2.2. Neuropsychological assessment

Intellectual abilities were measured using the French-Canadian version of the Fifth edition of the Wechsler Intelligence Scale for Children (WISC-V) [44]. This instrument is the most widely used in the world to evaluate intelligence of children between 6 and 16 years of age[45]. The full-scale intellectual quotient (FSIQ) is the most representative of global intellectual functioning and is the most reliable score[46]. Primary index scores were derived, consisting of Verbal Comprehension Index, Visual Spatial Index, Fluid Reasoning Index, Working Memory Index, and Processing Speed Index.

Long-term verbal memory was measured with the francophone version of the California Verbal Learning Test for Children (CVLT-C) [47]. This task is addressed to children aged from 5 to 16 years and implies learning a repeated list of 15 categorizable words. This procedure allows to evaluate verbal learning abilities, as well as the integrity of the three main components of long-term memorisation (i.e., encoding, storage, and retrieval).

Sustained auditory attention was evaluated with the *Code Transmission* subtest of the Test of Everyday Attention for Children (TEA-Ch) [48]. Sustained attention was specifically chosen because poor performance in this area is one of the most frequent findings in ADHD cognitive profile[49]. During this task, children are asked to monitor a stream of digits (presented at a rate of one every 2 seconds) in order to detect the particular target sequence and then to report the digit that occurred immediately before. They have to maintain their attention for a prolonged period without external retroaction, thus soliciting sustained attention as described in neurocognitive models[50]. The Australian norms developed by Manly et al. [48] were used.

Parents answered 4 standardized questionnaires to assess day-to-day behaviors in their children: 1) Behavior Rating Inventory of Executive Function (BRIEF) [51] to trace a portrait of everyday executive function behaviors; 2) Child Behavior Checklist (CBCL) [52], a screening of psychopathology that investigates internalizing and externalizing difficulties; 3) Conners-3[53] to assess symptoms of ADHD, as well as common comorbid problems such as learning difficulties or oppositional defiant disorder, and 4) Social Responsiveness Scale-2nd Edition (SRS-2) [54], to

examine social deficits and symptoms associated with ASD. All questions are answered on Likert's scales. General psychometric properties (test-retest reliability and validity) of these instruments are good, ranging from adequate to excellent.

Finally, parents retrospectively assessed the level of irritability manifested by their children during KD's acute phase by comparing it to the irritability usually observed when they have a fever. We used a scale graduated from 0 (no more irritability than for usual fever) to 10 (extreme irritability). Ratings were interpreted as follow: 0 = no irritability, 1-3 = low irritability, 4-7 = medium irritability and 8-10 = elevated irritability. This parameter was considered as a clinical measure of acute neurological implication.

2.3. EEG recording

The EEG recording was performed in a dark soundproof experimental chamber and brain activity was measured during a 3-minute eyes-open resting condition. The resting-state EEG data were acquired at the beginning of a session containing multiple EEG tasks and lasting approximately 45 minutes (data not presented). Eyes-closed condition is particularly difficult to maintain in younger children; they tend to squeeze their eyes, blink, or physically tense up, resulting in a signal of lower quality. Therefore, eyes-open condition was chosen for further analysis.

A high-density EEG system containing 128 electrodes was used for continuous recording (Electrical Geodesics System Inc., Eugene, OR, USA). Signals were acquired using an EGI Net Amp 300 amplifier and saved with NetStation EEG Software (Version 4.5.4) on a G4 Macintosh computer. EEG data were acquired at a 1000 Hz sampling rate and a bandpass filter of 0.1-500 Hz (Nyquist frequency) was applied. Electrodes were referenced to the vertex (Cz) during recording and impedances were maintained below 40 kΩ[55].

2.4. EEG processing

a) Pre-processing

Off-line pre-processing was carried out with MATLAB (version R2019b) and EEGLAB toolbox (v.14.1.2) [56]. Data were filtered with a 150 Hz low pass filter, a 0.5 Hz high pass filter, and a 60-Hz notch filter. Twenty-eight electrodes around the neck and face containing muscular artifacts were removed for all participants. Electrodes with a total standard deviation of <2μV and >200μV were automatically removed. Remaining noisy electrodes were manually rejected during visual

inspection. Data were then re-referenced to an average reference. Eye movement artifacts (blinks and saccades) and cardiac activity were removed using the semi-automatic independent component analysis tool. No group differences were found in the average of rejected components (1.71 vs 1.50 for CO, $p = 0.494$). Data were then segmented into 2-s epochs with 50% overlap, as necessary for window correction in pre-analyses[57]. Trials containing electrodes with spontaneous voltage amplitudes of >200 μV and ≤-200 μV were tagged and artifacted epochs were manually removed during subsequent visual inspection. There were no group differences in the average of data epochs that were retained (184 vs 190 for CO, $p = 0.676$). Participants with less than one minute of artifact free data were automatically rejected from the study (one girl from KD group was excluded).

b) Oscillatory power spectrum markers

Power spectral density (PSD) was calculated using Fast Fourier Transform with a Hanning window. The final PSD segments contained frequencies between 0.5 and 100 Hz with a resolution of 0.5 Hz. The cortical regions of interest were composed of left frontal (F3; E19, E20, E23, E24, E27, E28), right frontal (F4; E3, E4, E117, E118, E123, E124), frontocentral (FCz; E5, E6, E12, E13, E112), central (Cz; E7, E31, E55, E80, E106), parietal (Pz; E58, E59, E65, E90, E91, E96), and occipital (Oz; E70, E71, E74, E75, E76, E82, E83). These regions were determined based on recent literature on TBR and alpha peak[28, 33, 34, 57-59].

To obtain the TBR in each region of interest, we used the classical method of dividing theta-band (4-8 Hz) absolute power by beta-band (13-30 Hz) absolute power[31].

The APF corresponded to the frequency displaying the highest power value within the extended 6.5 – 12.5 Hz alpha band and had to be preceded and followed by lower power amplitudes. This method was applied to assure that true peaks were identified rather than random maximal values at the alpha band's boundary. Also, alpha's lower boundary was adjusted to account for reduced peak frequencies in children compared to adults. The amplitude of the alpha peak (APA) was measured in V^2/Hz. To better characterize and quantify the alpha peak saliency, we calculated a metric called the "alpha peak amplitude ratio" (APAR). This metric represents the ratio of the APA and the mean amplitude of the frequencies 1 Hz before and 1 Hz after the peak. Thus, a higher ratio represents a more prominent and well-defined alpha peak compared to neighbouring frequencies. The frequency range chosen was inspired by our peak distribution as well as by Chiang et al. [60] that

used a boxcar window of 1.83 Hz width in their best fitting model of the alpha peak parameters. The equation for the APAR is as follows:

$$\frac{APA}{[(\text{Amplitude}_{\text{APF}-1} + \text{Amplitude}_{\text{APF}+1})/2]}$$

Four other metrics used for a secondary analysis were computed on a slightly enlarged alpha range (6.0 Hz – 13.5 Hz) to characterize the profile of PSD curve: 1) Area under the curve; 2) Skewness (asymmetry of the distribution); 3) Maximum amplitude; 4) Maximum absolute slope (from the beginning of the curve to the apex).

2.5. Statistical analysis

In order to characterize the neuropsychological profile of our clinical cohort, we first described KD group's mean or median results on the cognitive tests and behavioral domains. Mean results were considered as corresponding to norms when they were in a range of ± 1 SD from normative average. We also used the tests norms and the thresholds established by original authors to calculate frequencies and proportions of participants with lower cognitive performances (i.e. standardized scores ≤ -1 SD) and/or with potential behavioral difficulties (i.e. borderline and clinical scores, standardized scores ≥ 1 SD).

The second objective of our study was to explore the integrity of the brain resting-state signals by comparing two electrophysiological markers (i.e. TBR and alpha peak) between the KD group and healthy children (CO group). Considering the small size of our clinical group, we assumed the non-normality of our data distribution and used nonparametric statistical tests. Continuous data (age, IQ, and EEG variables) were compared between groups using Mann-Whitney U test[61, 62]. This ranking test is used when data deviate from normal distribution patterns, or when the number of subjects in the two comparative groups are particularly different[63]. When significant differences were found, their effect size was calculated with Cohen's r[64, 65]. Categorical outcomes were compared using Fisher's exact test[66, 67].

Knowing the strong developmental trend in APF values, Spearman's correlations between APF and age were used as a measure of validity. These non-parametric correlations were also used to explore the association between the level of irritability in KD group during the inflammatory phase

of the disease and the TEA-Ch scaled score, Conners-3 Inattention T-score, and AP parameters. These specific variables were chosen because of the possible link between inflammation and ADHD[68] as well as because of the attentional symptomatology presented by our clinical cohort.

A secondary extended alpha range analysis was used to further investigate PSD curve profile differences between KD and CO. Alpha-band parameters were first aggregated from the six EEG sensing locations to form a 24-dimensional numerical vector for each subject. The t-distributed Stochastic Neighbor Embedding (t-SNE) dimensionality reduction technique[69] was then used to project the 24-dimensional feature vectors down to two for visualizing and quantifying possible groupings between KD and CO. This algorithm embeds high-dimensional data points in lower dimensions while conserving the relative similarities and dissimilarities found in the original hyperspace. Clustering analysis using k-mean[70] was then conducted within the KD group to investigate possible subgroups or characteristic phenotypes between KD patients. If subgroups were found, correlations of the members of each cluster with irritability levels or urine and blood serum findings were conducted. The following laboratory findings were considered: white blood cells, neutrophils, hematocrit, platelets, erythrocyte sedimentation rate, C-reactive protein, albumin, serum Na+, urine specific gravity (U density), and NTproBNP.

Statistical analyses were performed using SPSS statistics, version 25 (IBM Corp., Armonk, NY, USA). Given the exploratory nature of our analyses, we did not to correct for multiple testing and fixed the reported significance at $p < 0.05$.

3. Results

3.1. Patients' characteristics

The 15 patients (5 female, 13 Caucasians and 2 African Canadian) had been diagnosed and treated in Sainte-Justine's Health Center between 2009 and 2019, at the age of 3.9 ± 1.9 years old. They participated in this project at 8.8 ± 2.5 years old (4.9 ± 2.7 years after KD). Cardiac implication included myocarditis or pericarditis in 2, and coronary artery abnormalities in 3 (dilatation (Z score 2 - 2.5) in 2, and aneurysm (Z score ≥ 2.5) in 1). None of the patients were diagnosed with an acute neurological complication during the hospitalization. Demographic and medical characteristics of

our clinical cohort are described in Table 1. Main risk factors known to affect child development were gathered for each participant and can been seen in supplementary table S5.

3.2. Cognitive results

Figure 1 illustrates KD participants' individual cognitive performances, group mean, median, and normative data. Detailed individual performances can be found in online Supplementary data. One girl could not be reached for the neuropsychological evaluation.

a) Intellectual abilities

Proportions of KD participants with a score of 1 SD or more below national mean on the WISC-V primary indexes and global IQ were: 1) No participant (0%) for the Verbal Comprehension Index (VCI); 2) One participant (7%) for the Visuospatial Index (VSI); 3) One participant (7%) for the Fluid Reasoning Index (FRI); 4) Two participants (14%) for the Working Memory Index (WMI); 5) Four[1] participants (29%) for the Processing Speed Index (PSI) and 6) Two participants (14%) for the Full-scale IQ (FSIQ). Mean indexes were all within 1 SD of national norms (Figure 1A).

b) Verbal memory

Proportions of KD participants with results on the CVLT-C variables at or lower than 1 SD from norms were: 1) One participant (7%) for the total verbal learning (Total of trials 1-5); 2) One participant (7%) for the short-delay free recall; 3) One participant (7%) for the long-delay recall and 4) One participant (7%) for the recognition hits. As of the mean group results, all four variables corresponded to norms (for visual representation of the last three variables, see Figure 1B).

c) Auditory sustained attention

Four participants (29%) had a scaled score of 1 SD or more below the norm for the TEA-Ch's auditory sustained attention task (Code transmission subtest). Mean scaled score corresponded closely to the norms (Figure 1C).

[1] One of these four participants had many inversion errors during one of the tasks, which resulted in a lower score. Thus, its result may not reflect its true processing speed capacities and this proportion should be interpreted with caution.

3.3. Behavioral results

Parental ratings of behavioral difficulties were obtained using four standardized questionnaires. All norms are based on a general population sample, with a mean T-score of 50 and a SD of 10. In these scales, higher scores reflect higher probabilities of behavioral problems. We used the specific clinical thresholds as described in users' manual to determine whether a score was considered as borderline or clinical. Mean group results are shown in Table 2 (online) and individual scores can be consulted online in Supplemental data.

a) Executive functioning problems (BRIEF questionnaire)

According to parental ratings, the executive domain presenting the highest proportion of participants having borderline (i.e. ≥ 1 SD) or clinical (i.e. ≥ 1.5 SD) scores is the Working memory scale (7/14, 50%). Next, Organization of materials and Monitoring scales both indicated potential difficulty for three participants (21%). Two participants (14%) had borderline or clinical scores on the Initiative and Planification/organization scales. Finally, Inhibition, Shifting and Emotional control scales indicated borderline or clinical scores for one participant (7%) only.

Regarding composite indexes (i.e. combination of clinical scales presented above), the Behavioral index revealed a borderline score for one participant (7%) and the Metacognition index showed borderline or clinical score for three participants (21%). Only one participant (7%) was considered to have borderline result for the Global executive composite score (i.e. total of all clinical scales).

Group averages for all BRIEF scales and indexes scores were within 1 SD from norms, with the Working memory scale being the most elevated (57.00 ± 15.37).

b) Psychopathological, internal, and external difficulties (CBCL questionnaire)

Based on parental ratings, the syndromes scales with the highest proportions of children with borderline (≥ 1.5 SD) or clinical scores (≥ 2 SD) are the Anxious-depressed scale (3/14, 21%), followed by Withdrawal, Attention and Aggressivity problems (2/14, 14% for the three scales). The four remaining scales (i.e. Somatic complaints, Social problems, Thought problems and Rule-breaking behaviors) showed borderline or clinical scores for only one participant (7%).

Internalizing problems (i.e. sum of Anxious-depressed, Withdrawal, and Somatic complaints scores) were in the borderline (≥ 1 SD) or clinical (> 1.3 SD) range for four participants (29%).

Externalizing (sum of Rule-breaking and Aggressivity scores) and Total problems were both in this range for two participants (14%).

In regard to group results, mean T-scores of all scales were within 1 SD from norms, with highest means for the Attention problems (57.79 ± 9.85), Somatic complaints (56.71 ± 6.32), and Withdrawal (56.64 ± 6.68) scales.

c) Symptoms related to ADHD (Conners-3 questionnaire)

According to the parental responses, attentional concerns (i.e. T-scores in borderline [≥ 1 SD] or clinical [≥ 1.5 SD] range) were present for five children (36%) on the Conners-3 scale and for six children (43%) on the DSM-IV symptom scale. Hyperactivity-impulsivity concerns were indicated for five participants (36%) on the Conners-3 scale and for four children (29%) on the DSM-IV symptom scale. Defiance or aggressive behaviors were found for five children (36%). Four children (29%) could have an oppositional defiant disorder profile according to the DSM-IV symptom scale. Possible learning difficulties were indicated for three participants (21%). Global difficulties on the Conners-3 were shown for three children (21%). Finally, only one child (7%) showed possible difficulties with executive functioning and peer relations, and one with conduct disorder profile.

Considering group results, mean T-scores were all within 1 SD from, with highest means for attention difficulties on the Conners-3 scale (57.21 ± 14.99) and on the DSM-IV symptom scale (56.00 ± 12.34).

d) Symptoms related to Autism Spectrum Disorders (SRS-2 questionnaire)

Based on parents' answers on the SRS-2 questionnaire, three participants (21%) could have social communication difficulties (i.e. T-scores in borderline [≥ 1 SD] or clinical [≥ 1.5 SD] range), two participants (14%) could have social awareness difficulties, two participants (14%) could have social motivation difficulties, two participants (14%) could present restricted interests and repetitive behavior and only one (7%) could have social cognition difficulties. Global social and total difficulties were in the clinical range for one participant (7%) only.

Group results showed mean T-scores within 1 SD from norms for all scales, with highest means found in the social communication (49.57 ± 9.51) and restricted interests (49.14 ± 11.04) scales.

3.4. Irritability level during KD acute phase

Parents retrospective assessment showed a wide range of irritability levels during the acute phase (see Supplemental document for individual irritability scores). Of the 15 patients, 5 (33%) were not labeled with unusual irritability for the febrile status, 1 (6%) was labeled with low irritability, 2 (13%) with medium irritability, and 7 (47%) with high irritability. Of the last 7 participants, 5 had a maximal level of irritability (rating of 10/10). No significant correlations were found between the level of irritability during the acute phase of KD and neuropsychological measures of attention (TEA-Ch scaled score and Conners-3 Inattention T-score). However, qualitatively, we observed that 3 of the 5 participants with maximum irritability obtained a scaled score ≤ 1 SD below the mean on the TEA-Ch's sustained attention task.

3.5. EEG results

One girl form KD group was excluded from analysis due to unreadable data. EEG measurements of the remaining fourteen participants were compared to 32 healthy controls (CO group; 23 males, mean age = 8.9 ± 2.1 years old). KD and CO groups were similar in terms of sex distribution ($p = 0.742$, Fisher's exact test), age ($U = 223.5$, $p = 0.706$), and FSIQ ($U = 182.5$, $p = 0.321$). EEG outcomes and associated p-values are shown in Table 3.

a) Theta/beta ratio

No significant differences ($p > 0.05$) were found between KD and CO mean TBR in the 6 regions of interest.

b) Alpha peak

Participants with no clear alpha peak were excluded from analysis in the concerned region of interest. Absence of a clear peak was reported for 2/14 KD participants and 3/32 CO participants in left frontal (F3) region, for 2/14 and 2/32 for right frontal (F4) region, for 1/14 and 4/32 for frontocentral (FCz) region, for 2/14 and 3/32 in central (Cz) region and lastly, for 1/14 and 1/32 for parietal (Pz) region. All participants had a clear peak in the occipital (Oz) region.

As expected, moderate to strong positive correlations were found between APF and age, but only in the CO group in 5/6 regions of interest (Cz [$r_s(27) = 0.437$, $p = .018$], F3 [$r_s(27) = 0.480$, $p = 0.008$], FCz [$r_s(26) = 0.402$, $p = 0.034$], Pz [$r_s(29) = 0.358$, $p = 0.048$] and Oz [$r_s(30) = 0.460$,

$p = 0.008$]). The absence of correlation in KD group might be explained by a lack of statistical power, and thus the association between APF and age in KD should be investigated in a larger sample.

The APF and APA were not different between KD and CO groups. APAR (Figure 2) was significantly lower for the KD group in 4/6 regions, indicating a less prominent peak: FCz ($U = 78$, $p = 0.003$, $r = -.46$), Cz ($U = 101$, $p = 0.036$, $r = -.33$), Pz ($U = 99$, $p = 0.008$, $r = -.40$), and Oz ($U = 108$, $p = 0.006$, $r = -.41$). Effect sizes were medium to large[64]. No correlations were found between these three EEG parameters and acute irritability levels.

c) Extended alpha-range curve profiling

The projection of the high-dimensional PSD curve metrics down to two dimensions illustrates poor groupings and separation of the KD and CO subjects (Figure 3A). However, within the KD group, there is an apparent clustering of two subgroups following an embedding at the north-east quadrant and another at the south-west. Isolating only KD patients and recomputing the t-SNE projection on them reveals two well defined clusters (KD1 and KD2; Figure 3B). Ranking of features revealed that skewness in Cz and slopes in Cz and FCz regions had the most important contribution in clustering. These three features shown a negative polarity in KD2, indicating an attenuated alpha curve in this group. Interestingly, Fisher's exact test showed a significantly higher number of participants with irritability in this KD2 subgroup (8 vs 1, $p = 0.023$; Figure 3C). Further analysis to correlate the members of each cluster with irritability levels or urine blood serum findings revealed a trending but non-significant ($p = 0.06$) association of the KD2 phenotype with higher irritability scores. None of the urine or blood serum markers were significantly different between the two subgroups (see Supplemental data for exact p-values).

4. Discussion

The goal of our study was to describe and explore potential medium to long-term consequences of KD on neuropsychological and electrophysiological development. Neuropsychological evaluation of intellectual abilities, verbal memory, and auditory sustained attention was conducted in primary-school aged children with past KD. Their behavioral capacities were evaluated using four parental inventories assessing executive functioning, internalized and externalized difficulties, attention and

hyperactivity, and symptoms related to Autism Spectrum Disorder (ASD). The theta/beta ratio (TBR) and the alpha peak (AP) parameters were extracted from resting-state EEG power spectrum and compared to matched healthy controls.

4.1. Neuropsychological development

a) Cognition

This pilot study found overall preserved intellectual abilities in a small sample of children with previous KD, as in accordance with past literature[11, 16, 17].

Furthermore, our results provide preliminary indication of adequate verbal memory and learning capacities in these children.

Nevertheless, our results still showed an important proportion of children with lower performances in the sustained attention task (4/14, 29%). To our knowledge, this is the first study to highlight possible attentional difficulties after the disease using objective testing. Early detection of sustained attention deficits in children is important, as it can affect most everyday tasks, with impacts on academic results, social communication, and mental health[71]. Additional measures of attention subtypes (i.e., sustained, selective, and divided) using the other subtests of the TEA-Ch or the well-known Conners' Continuous Performance Test[72] could provide more details about the attentional profile of children with an history of KD.

b) Behavior

In terms of executive functioning at home, potential difficulties in working memory, a cognitive function that is closely related to attention, were reported in half of our clinical cohort. Children with weaker abilities in these cognitive domains often struggle with remembering things even for a few seconds, have trouble with mental manipulation (e.g., solving orally presented arithmetic problems), have difficulty following long conversations, or forget what they are supposed to do[51].

Internalized difficulties such as anxiety, depression or withdrawal symptoms were found in 29% of our study sample. While a little less than the 40% previously reported by Carlton-Conway and colleagues[12], this proportion is still significant. This difference could be explained by sample characteristics such as age (3-18 years old in Carlton-Conway), as well as differences in long-term management since the former study was published in 2005. As such, the American Heart

Association now recommends establishing a psychological screening, assessment, and intervention for KD patients[3]. Therefore, greater awareness among paediatricians and other professionals about possible behavioral sequelae after KD may generate increased support and earlier mental health referrals. Nevertheless, there is still a considerable percentage of children that could potentially beneficiate from further psychological follow-up.

Parental concerns regarding attentional capacities were considerable, with 43 and 50% of borderline or clinical scores. Hyperactivity-impulsivity was also elevated in our sample (29-36%). Therefore, parental answers highlighted a pattern of difficulties in some participants that were compatible with what is found in a neurodevelopmental disorder like ADHD. When looking at the correspondence between these reported measures and the sustained attention scores, we see that 3 out of 4 participants with lower performance were considered as having attention difficulties in their everyday lives by their parents. Authors have established that performance-based and reported measures of cognition capture two different levels of mental constructs: the efficiency of cognitive processes in standardized testing, and success in goal pursuit in parental assessment. Comprehensive neuropsychological assessment should thus continue to include both types of measures[73]. While previous studies investigating the association between ADHD and KD have shown inconsistent outcomes, [19-21] our results highlight the relevance of pursuing this research.

Finally, social impairment and restricted interests or behaviors were rare, thus not supporting an association between KD and symptoms of ASD. Individual data indicate that the two same children were considered with potential behavioral difficulties on almost all the standardized questionnaires.

4.2. Electrophysiological outcome

a) Theta/beta ratio

Our pilot study didn't reveal differences in TBR values after KD. As such, no outliers were found, and KD group averages (2.88 – 3.66 range) across scalp regions were coherent with results reported in Arns et al. [28] meta-analysis. There was a trend with KD group having higher TBR in 5 of the 6 regions considered, but it was not significant. Also, the TBR is mainly studied in individuals with an official ADHD diagnosis, in which attentional deficits are of important magnitude. Therefore, it is possible that attentional difficulties in our clinical cohort were too subtle to be detected in their

brain's electrophysiological signature. More recently, a new interpretation suggesting that TBR could be associated with cognitive processing capacity rather than with arousal and attention has been proposed[74]. Further studies are thus needed to better capture the TBR's cognitive correlates.

b) Alpha peak and extended alpha-range curve profiling

Finally, our study provides preliminary indication of a less prominent AP in children with previous KD. This attenuation was found in four midline scalp regions during eyes-open resting state. Using a simple quantitative metric to quantify the AP saliency compared to adjacent signal, we revealed subtle differences in AP slope in KD patients. As this biomarker reflects the integrity of neural networks, this difference suggests that the disease could impact brain electrophysiological signals even years after its onset. This EEG finding may be of clinical relevance and more studies are needed to further support this preliminary finding. Further analysis of the extended alpha band using a reduction algorithm revealed a clear clustering of our KD participants in two subgroups, with the cluster containing more participants with acute irritability also being the one with a globally weaker AP. This suggests that EEG abnormality may be predominant in children that demonstrated irritability during KD inflammatory phase. It highlights the importance of monitoring irritability levels at admission, as this clinical measure may reflect not only acute neurological implications, but also the risk of long-term consequences on electrophysiological signals. To our knowledge, no other studies have investigated the association of this "neuroinflammatory" induced irritability with altered EEG signals. Previous literature has shown resting-state EEG abnormalities in chronic inflammatory diseases such as rheumatoid arthritis[75], asthma[76], and depression[77] but without the presence of extreme irritability. Only one study by Balter and al. [78] has shown that acute inflammation does not affect attentional performances, but still leads to an enhanced suppression of the alpha band power. Thus, the brain had to compensate and exert greater cognitive effort in order to maintain an adequate performance. In sum, more studies are needed to corroborate the utility of the irritability as a neurological marker and to help understanding the underlying electrophysiological mechanism.

4.3. Pathological mechanisms associated with long-term sequelae

Cerebral hypoperfusion has been documented in KD[23, 24]. As shown by Hikita et al. [24], hypoperfusion can last for several months or even years after KD acute phase. Therefore, it was suggested that the impact on cerebral blood flow could accumulate and eventually result in

neuropsychiatric symptoms. Carlton-Conway et al. [12] also hypothesized that behavioral deficits would result from cerebral vasculopathy, rather than solely from the psychological complications of having a rare acute illness. They suggested that a potential remodelling process in the brain, similar to remodeling of coronary arteries after an aneurysm, could continue for many years and thus lead to changes in children's behavior. Another possible explanation is the impact of the elevated cerebrospinal fluid inflammatory factors on white matter integrity[79]. Previous work evaluating the impacts of inflammation on cognition has shown excessive production of IL-6 in association with altered neurotransmission in cerebral structures that are essential to cognition, such as the prefrontal cortex[80]. Consistent with that finding, inflammation has been associated with lower performance in attentional tasks, executive functions, and has been linked to the etiology of ADHD[68, 81-83].

4.4. Strengths and limitations

By evaluating numerous cognitive and behavioral abilities, this pilot study provides a unique in-depth characterization of neuropsychological development in a series of children with past KD. Objective testing of specific cognitive domains such as long-term verbal memory and sustained attention also adds to the contribution of our study. Furthermore, parental evaluation of irritability during the acute and subacute phases of the disease is a promising measure that could help clinicians better capture neurological implications in their patients. This clinical tool could be easily implemented in KD clinical management in a better quantitative manner. Finally, to our knowledge, this is the first study to investigate electrophysiological markers in this population. EEG is a sensitive, non-invasive, and low-cost technique that helped unveil subtle impacts of KD on a well-established maturational biomarker like the alpha peak. This finding, combined with the fact that KD can impact the brain even in patients without neurological symptoms, highlights the relevance of assessing cerebral integrity in long-term KD follow-up as well as during the sub-acute phase of the disease.

To examine new developmental outcomes in KD, this study used a descriptive and exploratory form. The main limitation of our study is the small sample size, resulting in low statistical power and limited possible statistical tests. While this number of participants was appropriate for a pilot study, future studies require larger clinical groups to confirm or refute presented results. Due to the exploratory nature of our analyses, no correction for multiple comparisons were made, but would

be necessary in larger studies. Also, retrospective assessment of irritability might have been susceptible to a certain recall bias by parents, as this measure was taken years after the disease. Although taking a step back from this stressful event may have helped parents answering this question with less emotions involved, future studies should consider having multiple reports of irritability level (i.e., during the subacute phase when symptoms are stable and retrospectively months or one year after to see if the parents' perspective has changed). Existing scales such as the Richmond Agitation-Sedation Scale[84] could also be used by health professionals to help reducing the possibilities of subjective evaluation. If extreme irritability is indeed reflecting the central nervous system involvement, analyses of brain inflammatory factors could also help deepen our understanding of this promising variable. Furthermore, adding a medical control group (e.g. children that have been hospitalized or with rheumatic conditions) could help isolate more specific outcomes related to KD. Since no other studies on EEG markers after KD have been published, our explanation of the pathophysiological phenomenon leading to a less salient alpha peak remains limited. Furthermore, specialists that participated to data collection and/or analysis were not blind to the participants' group affiliation. Also, lower memory performances were found in the same participant. According to the design of this study, it is difficult to determine whether these scores were really attributed to memory weaknesses or to psychological factors such as anxiety and shyness. Finally, considering that all participants were recruited from the same site, generalization of these results into different clinical cohorts remains to be investigated.

4.5. Recommendations and perspectives

In terms of neuropsychological development, our preliminary results support the relevance of pursuing the investigation of possible attentional impacts after KD. Inclusion of teacher's perspective about participants' attention and general behavior in class could promote a richer perspective. Further evaluation of executive functions and attention with standardized testing, as well as a diagnostic interview by a trained neuro/psychologist could help determine if children's profiles are consistent with ADHD. Consideration of parental stress using tools such as the Parenting Stress Index[80] could also help understanding the impact of KD on familial interactions. Also, a longitudinal study starting after KD's acute phase could help to better capture and characterize electrophysiological impacts of the disease. This could also contribute to see if the impact on the alpha peak is already present in the subacute phase or rather declared later with brain

maturation. Furthermore, using EEG tasks with active stimuli or tasks could help explore cerebral mechanisms that are related to different cognitive processes.

5. Conclusion

This pilot study shows preserved intellectual abilities and verbal memory functions in primary school-level Quebec children with previous history of KD. Attention deficit concerns were more readily reflected from parents' assessment as well as in neuropsychological testing. The association between KD and attentional difficulties merits further investigation. In accordance with previous studies, we found a high incidence of reported internalized difficulties in our clinical cohort, mainly anxiety symptoms. Our results highlight the relevance of including screening questions about behavioral issues in children in the long-term management of KD. Referral to clinical psychologists or neuropsychologists may be more frequently needed than previously anticipated. This first EEG-based study in context of KD provides preliminary indication of long-term impact on maturational electrophysiological signals. As such, a less prominent alpha peak in central regions was found years after the acute illness, predominantly in children with acute irritability. However, no associations between this marker and cognitive or behavioral outcomes were found. Therefore, larger future studies are needed to better capture the clinical implications of this finding. Finally, earlier characterization of brain inflammation factors during the acute and subacute stages, as well as the use of cerebral imagery, could help unveil pathophysiological mechanisms leading to altered EEG signals.

This pilot study represents a first step towards a more comprehensive assessment of neurocognitive development after KD. It aims to guide the parameters of future larger studies by identifying variables of particular interest in long-term management of KD. Further research is needed to corroborate these findings and to continue improving provided care.

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Tables

Table 1. Characteristics of the KD group

Characteristics	**Results** (N = 15)
Male: Female	10:5
Age at diagnosis (mean years ± SD)	3.9 ± 1.9
Age at testing (mean years ± SD)	8.8 ± 2.5
Interval of time since diagnosis (mean years ± SD)	4.9 ± 2.7
Ethnicity	
• **Caucasian**	13/15 (87%)
• **African Canadian**	2/15 (13%)
Annual household income (CAD$, N = 14)	
• **< 30 000**	1/14 (7%)
• **30 000 – 60 000**	1/14 (7%)
• **> 60 000 – 100 000**	5/14 (36%)
• **> 100 000**	7/14 (50%)
Clinical features of KD	
• **Duration between fever onset and treatment (mean days ± SD)**	6.6 ± 1.7
○ **Degree of fever at admission (mean °C ± SD)**	39.7 ± 0.6

• **Erythematous rash**	14/15 (93%)
• **Oral changes**	11/15 (73%)
• **Bilateral conjunctivitis**	15/15 (100%)
• **Extremity changes**	11/15 (73%)
• **Cervical lymphadenopathy**	7/15 (47%)
Cardiovascular implications	5/15 (33%)
• **Myocarditis or pericarditis**	2/5 (40%)
• **Coronary abnormalities**	3/5 (60%)
○ **Coronary dilatation (Z score >2 to < 2.5)**	2/3 (66%)
○ **Coronary aneurysm (Z score ≥ 2.5)**	1/3 (33%)
Musculoskeletal implications (arthritis)	2/15 (13%)
Gastrointestinal implications	6/15 (40%)
Laboratory results (mean ± SD)	
• **ESR (mm/H)**	54.36 ± 16.95
• **CRP (mg/L)**	162.35 ± 87.25
• **NT-proBNP (pg/ml)**	5117.20 ± 8225.58
IVIG administration (2g/kg dosage)	15/15 (100%)
• **IVIG resistance (administration of a second dose)**	5/15 (33%)

Note. KD: Kawasaki disease, ESR: Erythrocyte Sedimentation Rate, CRP: C-reactive protein, NT-proBNP: N-terminal pro-brain natriuretic peptide, IVIG: intravenous immunoglobulin

Table 2. Behavioral results of KD group

Behavioral measures	BRIEF scales										
	Inhibition	**Shifting**	**Emotional Control**	**Initiative**	**Working Memory**	**Planification - Organization**	**Organization of materials**	**Monitoring**	**Behavioral Regulation Index**	**Metacognition Index**	**Global Executive Composite**
Mean (SD)	42.71 (15.06)	45.93 (9.75)	44.36 (9.16)	49.64 (11.82)	57.00 (15.37)	47.08 (10.33)	51.29 (8.61)	46.21 (13.28)	44.00 (9.45)	49.57 (10.41)	46.71 (9.26)
Borderline or clinical scores	1/14	1/14	1/14	2/14	7/14	2/14	3/14	3/14	1/14	3/14	1/14

Behavioral measures	CBCL scales										
	Anxious-Depressed	**Withdrawal**	**Somatic Complaints**	**Social Problems**	**Thought Problems**	**Attentional Problems**	**Rule-Breaking**	**Aggressivity Problems**	**Internalizing Problems**	**Externalizing Problems**	**Total Problems**
Mean (SD)	55.86 (8.93)	56.64 (6.68)	56.71 (6.32)	55.50 (8.66)	54.50 (7.00)	57.79 (9.85)	52.86 (4.79)	54.71 (6.83)	53.86 (11.94)	47.57 (11.90)	48.71 (14.88)
Borderline or clinical scores	3/14	2/14	1/14	1/14	1/14	2/14	1/14	2/14	4/14	2/14	2/14

Behavioral measures	Conners-3 scales										
	Content scales							DSM-IV symptom scales			
	Inattention	Hyperactivity -Impulsivity	Learning Difficulties	Executive functioning	Defiance-Aggression	Peer Relations	Global Index	ADHD Inattentive	ADHD Hyperactive-Impulsive	Conduct Disorder	Oppositional Defiant Disorder
Mean (SD)	57.21 (14.99)	55.07 (15.76)	51.79 (14.09)	49.08 (9.79)	53.21 (12.38)	50.14 (12.87)	53.64 (12.79)	56.00 (12.34)	53.93 (15.63)	47.29 (5.81)	54.07 (14.72)
Borderline or clinical scores	5/14	5/14	3/14	1/14	5/14	1/14	3/14	6/14	4/14	1/14	4/14

Behavioral measures	SRS-2 scales						
	Social awareness	Social cognition	Social communication	Social motivation	Restricted interests and repetitive behavior	Social Total	Global Total
Mean (SD)	48.36 (8.98)	47.64 (8.21)	49.57 (9.51)	48.43 (7.48)	49.14 (11.04)	48.50 (8.64)	48.57 (8.90)
Borderline or clinical scores	2/14	1/14	3/14	2/14	2/14	1/14	1/14

Note. BRIEF: Behavior Rating Inventory of Executive Functions, CBCL: Child Behavior Checklist, SRS-2: Social Responsiveness Scale-2. All results are T-scores, with a normative mean = 50 and standard deviation = 10.

Table 3. Electrophysiological outcomes

Characteristics		Groups		p-value
		KD (N = 14)	CO (N = 32)	
		Mean (SD)		
Theta/beta ratio	F3	3.07 (0.78)	2.93 (0.71)	.504
	F4	2.88 (0.68)	2.91 (0.63)	.877
	FCz	4.18 (0.89)	3.82 (0.86)	.262
	Cz	3.66 (0.78)	3.41 (0.81)	.352
	Pz	3.35 (0.66)	3.13 (0.73)	.504
	Oz	3.18 (0.67)	3.09 (0.74)	.294
Alpha peak frequency (Hz)	F3	8.63 (1.45)	9.29 (1.09)	.238
	F4	8.38 (1.40)	9.35 (1.05)	.042*
	FCz	9.54 (2.01)	9.52 (.094)	.836
	Cz	8.63 (1.17)	9.33 (1.12)	.078
	Pz	8.96 (1.86)	9.55 (0.83)	.265
	Oz	8.96 (1.77)	9.47 (0.88)	.298
Alpha peak amplitude (V^2/Hz)	F3	0.84 (0.54)	0.85 (0.31)	.524
	F4	0.88 (0.39)	0.84 (0.28)	.419
	FCz	0.70 (0.34)	0.73 (0.32)	.793

	Cz	0.68 (0.38)	0.66 (0.20)	.788
	Pz	0.72 (0.40)	0.71 (0.38)	.928
	Oz	1.05 (0.60)	1.00 (0.58)	.535
Alpha peak amplitude ratio	F3	1.20 (0.18)	1.32 (0.22)	.078
	F4	1.21 (0.15)	1.29 (0.19)	.150
	FCz	1.15 (0.13)	1.32 (0.23)	.003**
	Cz	1.21 (0.21)	1.35 (0.23)	.036*
	Pz	1.15 (0.13)	1.27 (0.17)	.008**
	Oz	1.17 (0.12)	1.28 (0.15)	.006**

Note. Number of observations for the alpha peak in each scalp region: 12/14 and 29/32 in F3, 12/14 and 30/32 in F4, 13/14 and 28/32 in FCz, 12/14 and 29/32 in Cz, 13/14 and 31/32 in Pz, and 14/14 and 32/32 in Oz. *$p < .05$ **$p < .01$ using Mann-Whitney U test.

SUPPLEMENTARY TABLES

Table S1. Individual and mean cognitive results of KD group

Participants	WISC-V Indexes						CVLT-C				TEA-Ch
	VCI	VSI	FRI	WMI	PSI	FSIQ	Total trials 1-5	Short-delay free recall	Long-delay free recall	Recognition hits	Code transmission subtest
KDN001	92	92	121	112	100	102	53	1,5	1	0,5	9
KDN002	98	92	94	**85**	108	93	52	1,5	1	0	**5**
KDN003	92	102	97	94	**63**	**84**	**30**	0	**-2**	**-1,5**	8
KDN005	113	97	109	100	**83**	105	47	1,5	1	1	10
KDN006	98	100	106	**76**	100	94	41	0,5	0	0,5	**5**
KDN007	133	119	106	120	103	121	59	1,5	2	0,5	8
KDN008	100	97	115	117	**80**	109	62	0,5	0,5	0,5	8
KDN009	113	119	100	100	108	111	57	1	1,5	1	15
KDN010	103	111	100	97	119	110	57	0,5	0,5	0,5	**6**
KDN011	106	119	112	110	**83**	106	66	1	0,5	0,5	13
KDN012	86	**78**	**82**	97	105	**84**	52	-0,5	1	1	**7**
KDN013	103	114	103	97	123	107	54	1,5	0	0,5	13
KDN014	121	138	128	130	108	128	61	1	-0,5	0,5	14

KDN015	111	89	100	115	86	102	47	**-1,5**	-0,5	0,5	11
Mean (SD)	105 (13)	105 (16)	105 (12)	104 (15)	98 (17)	104 (13)	52.7 (9.3)	0.71 (0.89)	0.43 (1)	0.43 (0.62)	9.43 (3.32)

Note. WISC-V: Wechsler Intelligence Scale for Children-Fifth Edition, VCI: Verbal Comprehension Index, VSI: Visual Spatial Index, FRI: Fluid Reasoning Index, WMI: Working Memory Index, PSI: Processing Speed Index, FSIQ: Full-scale Intellectual Quotient. Wechsler scales' norms are standardized (mean=100 and standard deviation=15) based on a general population sample. CVLT-C: California Verbal Learning Test for Children results are z-scores (norms: mean=0 and SD = 1), excepted for Total trials 1-5 which is a T-score (norms: mean=50 and SD = 10). TEA-Ch: Test of Everyday Attention for Children, Code transmission result is expressed in scaled score (norms: mean =10 and SD=3).

Table S2. Individual and mean behavioral results for KD group

Participants	BRIEF scales										
	Inhibition	**Shifting**	**Emotional Control**	**Initiative**	**Working Memory**	**Planification - Organization**	**Organization of materials**	**Monitoring**	**Behavioral Regulation Index**	**Metacognition Index**	**Global Executive Composite**
KDN001	55	52	47	50	**65****	**62***	**61***	**70****	51	**63***	59
KDN002	58	**72****	43	**75****	**86****	N/A	59	58	56	57	57
KDN003	45	43	38	46	**73****	43	53	38	40	51	47
KDN005	30	43	38	52	48	50	56	41	36	49	44
KDN006	40	50	38	39	48	46	46	41	41	43	42
KDN007	38	37	35	39	40	39	46	38	34	39	36
KDN008	37	36	36	35	36	33	33	31	35	30	31
KDN009	36	50	40	42	35	37	46	32	39	37	37
KDN010	58	53	57	52	**63***	**67****	**63***	**70****	57	**65****	53
KDN011	37	36	38	44	**67****	35	58	34	36	48	42
KDN012[1]	**67****	50	**64***	**71****	**74****	47	48	46	**63***	58	**61***
KDN013	44	45	56	50	50	49	46	49	49	49	49
KDN014	40	38	51	59	**62***	58	**60***	**60***	42	**61***	55
KDN015	40	38	40	41	51	46	43	39	37	44	41

Mean (SD)	42.71 (15.06)	45.93 (9.75)	44.36 (9.16)	49.64 (11.82)	57.00 (15.37)	47.08 (10.33)	51.29 (8.61)	46.21 (13.28)	44.00 (9.45)	49.57 (10.41)	46.71 (9.26)

Table S2. Individual and mean behavioral results for KD group (continued)

Participants	**CBCL scales**										
	Anxious-Depressed	**Withdrawal**	**Somatic Complaints**	**Social Problems**	**Thought Problems**	**Attentional Problems**	**Rule-Breaking**	**Aggressivity Problems**	**Internalizing Problems**	**Externalizing Problems**	**Total Problems**
KDN001	51	54	50	51	50	61	50	50	48	40	46
KDN002	**78****	60	**72****	**82****	**75****	**83****	**66***	**68***	**75****	**68***	**75****
KDN003	**69***	58	53	58	51	61	57	61	**65***	60	61
KDN005	53	62	53	58	54	50	50	52	57	48	51
KDN006	50	50	50	50	50	50	50	50	41	33	26
KDN007	50	50	57	51	54	50	53	50	45	46	44
KDN008	50	50	50	50	50	50	50	50	34	33	24
KDN009	50	50	57	50	50	50	50	50	45	33	34
KDN010	53	58	53	56	51	61	51	59	54	56	55
KDN011	50	54	61	50	50	53	50	50	50	44	43
KDN012	57	**70****	64	62	62	**73****	59	**68***	**66***	**66***	**69***
KDN013	**67***	**69***	62	58	56	56	54	58	**69****	56	61
KDN014	54	54	58	51	51	59	50	50	55	43	49

KDN015	50	54	54	50	59	52	50	50	47	40	44
Mean (SD)	55.86 (8.93)	56.64 (6.68)	56.71 (6.32)	55.50 (8.66)	54.50 (7.00)	57.79 (9.85)	52.86 (4.79)	54.71 (6.83)	53.86 (11.94)	47.57 (11.90)	48.71 (14.88)

Table S2. Individual and mean behavioral results for KD group (continued)

Participants	**Conners-3**										
	Conners-3 content scales							**DSM-IV symptom scales**			
	Inattention	**Hyperactivity -Impulsivity**	**Learning Difficulties**	**Executive functioning**	**Defiance-Aggression**	**Peer Relations**	**Global Index**	**ADHD Inattentive**	**ADHD Hyperactive-Impulsive**	**Conduct Disorder**	**Oppositional Defiant Disorder**
KDN001	58	**65****	55	46	50	43	56	56	**64***	43	49
KDN002	**>90****	**>90****	**>90****	**76****	**71****	**>90****	**85****	**80****	**89****	57	**73****
KDN003	**80****	**69****	**65****	44	**67****	44	58	**68****	**66****	52	**64***
KDN005	54	52	50	49	**67****	58	51	58	47	52	**67****
KDN006	41	<40	42	<40	43	44	<40	<40	<40	47	41
KDN007	44	51	46	47	43	44	47	46	47	47	44
KDN008	<40	<40	<40	<40	44	43	<40	<40	<40	45	41
KDN009	<40	<40	<40	<40	42	58	44	<40	<40	<40	44
KDN010	**70****	**63***	47	50	47	44	**67****	**63***	58	44	47
KDN011	59	52	<40	47	42	44	45	**61***	52	44	44

KDN012	**61***	**78****	**67****	54	**76****	53	**68****	**70****	**80****	**60***	**>90****
KDN013	53	47	55	47	**61***	53	56	52	48	43	57
KDN014	**62***	43	43	59	49	42	52	**62***	43	44	55
KDN015	49	41	45	45	43	42	42	48	41	44	41
Mean (SD)	57.21 (14.99)	55.07 (15.76)	51.79 (14.09)	48.86 (9.45)	53.21 (12.38)	50.14 (12.87)	53.64 (12.79)	56.00 (12.34)	53.93 (15.63)	47.29 (5.81)	54.07 (14.72)

Table S2. Individual and mean behavioral results for KD group (end)

Participants	**SRS-2 scales**						
	Social awareness	**Social cognition**	**Social communication**	**Social motivation**	**Restricted interests and repetitive behavior**	**Social Total**	**Global Total**
KDN001	53	49	44	49	46	47	47
KDN002	**62***	**69****	**67****	**60***	**80****	**67****	**70****
KDN003	48	52	56	52	46	53	52
KDN005	51	52	56	56	48	55	53
KDN006	32	39	39	44	43	38	39
KDN007	45	46	46	42	43	44	44
KDN008	51	39	38	38	41	39	39
KDN009	48	44	45	42	43	44	43

KDN010	**60***	53	55	46	50	54	53
KDN011	35	48	41	40	46	41	42
KDN012	59	45	**62***	49	**68****	55	58
KDN013	50	53	**60***	**62***	46	58	56
KDN014	38	39	40	44	45	39	40
KDN015	45	39	45	54	43	45	44
Mean (SD)	48.36 (8.98)	47.64 (8.21)	49.57 (9.51)	48.43 (7.48)	49.14 (11.04)	48.50 (8.64)	48.57 (8.90)

Note. BRIEF: Behavior Rating Inventory of Executive Function, CBCL: Child Behavior Checklist, DSM-IV: Diagnostic and Statistical Manual of Mental Disorder-Fourth edition, SRS-2: Social Responsiveness Scale-2. Results are shown in T-scores (norms are mean=50 and standard deviation=10 based on a general population sample). Higher scores represent higher difficulties.

[1]Possible inconsistency. *Borderline range; **Clinical range

Table S3. Individual irritability levels (compared to usual fever) during KD acute phase, as retrospectively assessed by parents.

Participants (N = 15)	Irritability levels (1-10 range)
KDN001	2
KDN002	10
KDN003	0
KDN004	8
KDN005	0
KDN006	0
KDN007	6
KDN008	0
KDN009	5
KDN010	10
KDN011	0
KDN012	10
KDN013	10
KDN014	8
KDN015	10

Note. Higher scores reflect higher irritability.

Table S4. p-values for urine and serum blood markers between KD1 and KD2 subgroups

Urine and blood serum marker	KD1 (mean ± SD)	KD2 (mean ± SD)	p-value
White blood cells (cell/mm^3)	20.23 ± 7.97	15.23 ± 6.25	0.22
Neutrophils (%)	70.60 ± 18.30	65.90 ± 26.51	0.73
Hematocrit (%)	28.04 ± 5.34	27.17 ± 5.31	0.77
Platelets (pt/mm^3)	754.80 ± 315.39	587.78 ± 234.99	0.28
Erythrocyte sedimentation rate (mm/H)	55.20 ± 12,46	52.38 ± 8.21	0.38
C-reactive protein (mg/L)	157.02 ± 84.15	144.16 ± 69.72	0.76
Albumin (g/L)	25.00 ± 7.11	24.38 ± 4.27	0.49
Serum Na+ (mmol/L)	137.00 ± 2.35	136.33 ± 2.00	0.58
Urine specific gravity (U density)	1.02 ± 0.01	1.02 ± 0.01	0.54
NTproBNP (pg/ml)	3210.00 ± 4174.25	4365.33 ± 8576.77	0.78

Table S5. Personal history of risk factors known to affect child development for each KD participant

Participants	**Risk factors**								
	Complications during pregnancy or at birth	Alcohol during pregnancy	Tobacco during pregnancy	Prematurity	Familial history of ADHD[e]	Familial history of anxiety or mood disorders	Familial history of intellectual disability	Familial history of autism	Familial history of academic difficulties
KDN001	No	No	Yes	No	No	No	No	No	No
KDN002	No	No	No	No	No	Yes	No	No	Yes
KDN003	Yes[a]	No	No	No	No	No	No	No	No
KDN005	No	No	Yes	No	No	No	No	No	No
KDN006	No	No	No	No	-	-	-	-	-
KDN007	No	No	No	No	No	Yes	No	No	No
KDN008	No	No	No	No	-	-	-	-	-
KDN009	No	No	No	No	-	-	-	-	-
KDN010	Yes[b]	No	No	No	Yes	Yes	No	No	Yes
KDN011	Yes[c]	No	No	No	No	No	No	No	Yes

KDN012	Yes[d]	No	No	No	No	Yes	No	No	Yes
KDN013	No	No	No	No	No	No	No	No	No
KDN014	No	No	No	Yes	No	Yes	No	No	No
KDN015	No	No	No	No	No	No	No	No	No
Total (n = 14*)	4	0	2	1	1	5	0	0	3

- : information not disclosed by parents

*One missing data

[a]Specific complications not disclosed by parents

[b]Uterine irritability

[c]Placental abruption

[d]Umbilical cord wrapped around the neck at birth

[e]First-degree relatives only

Figures

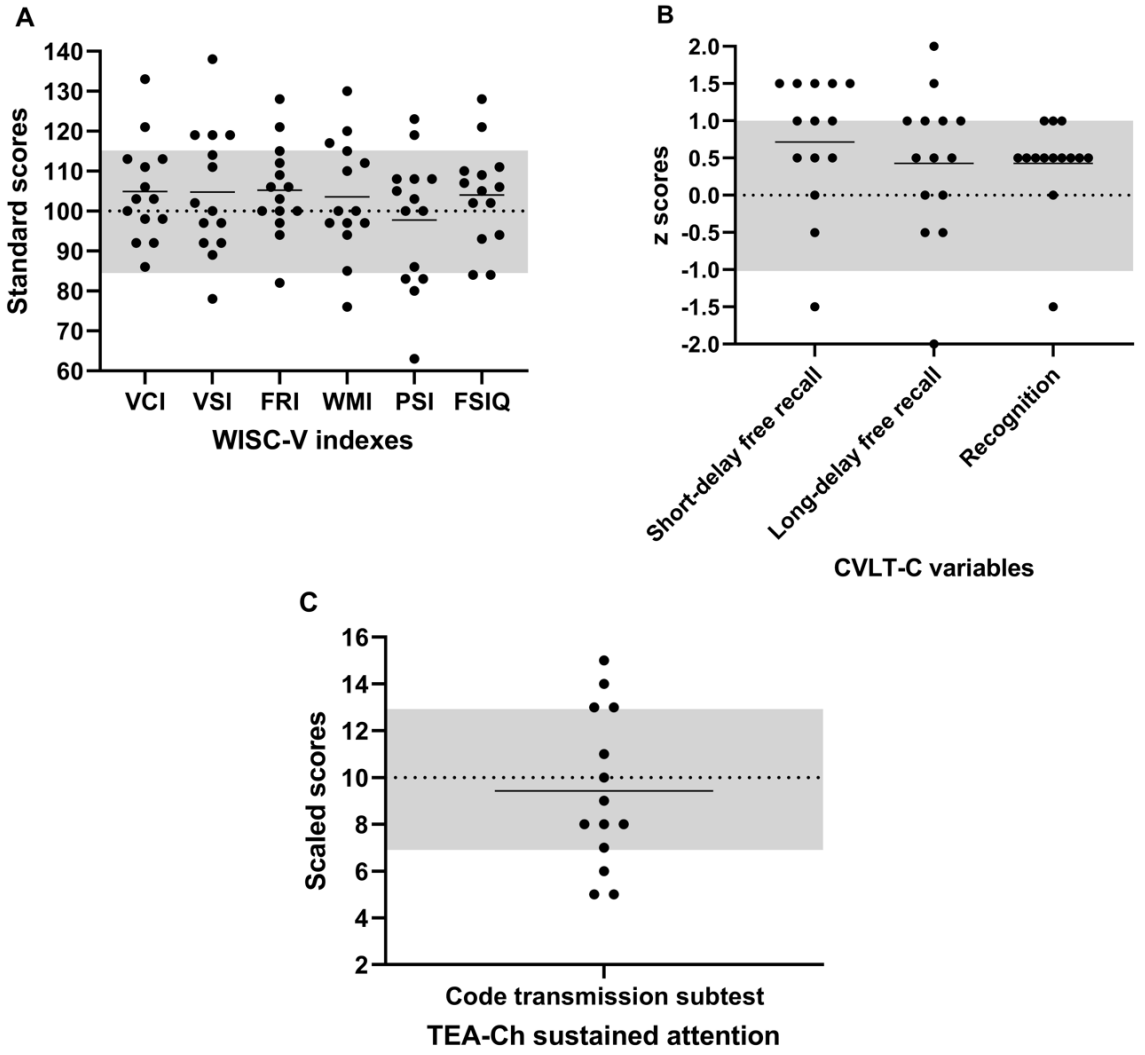

Figure 1. Cognitive performances of KD participants.

These scatter plots show individual scores (each point represents one KD participant), group mean (solid lines), group median (dashed lines), and normative mean (dotted lines). **(A)** WISC-V primary indexes and full-scale IQ, **(B)** CVLT-C variables, and **(C)** the TEA-Ch Code transmission subtest. The gray area represents the norms' average range (mean ± 1 SD).

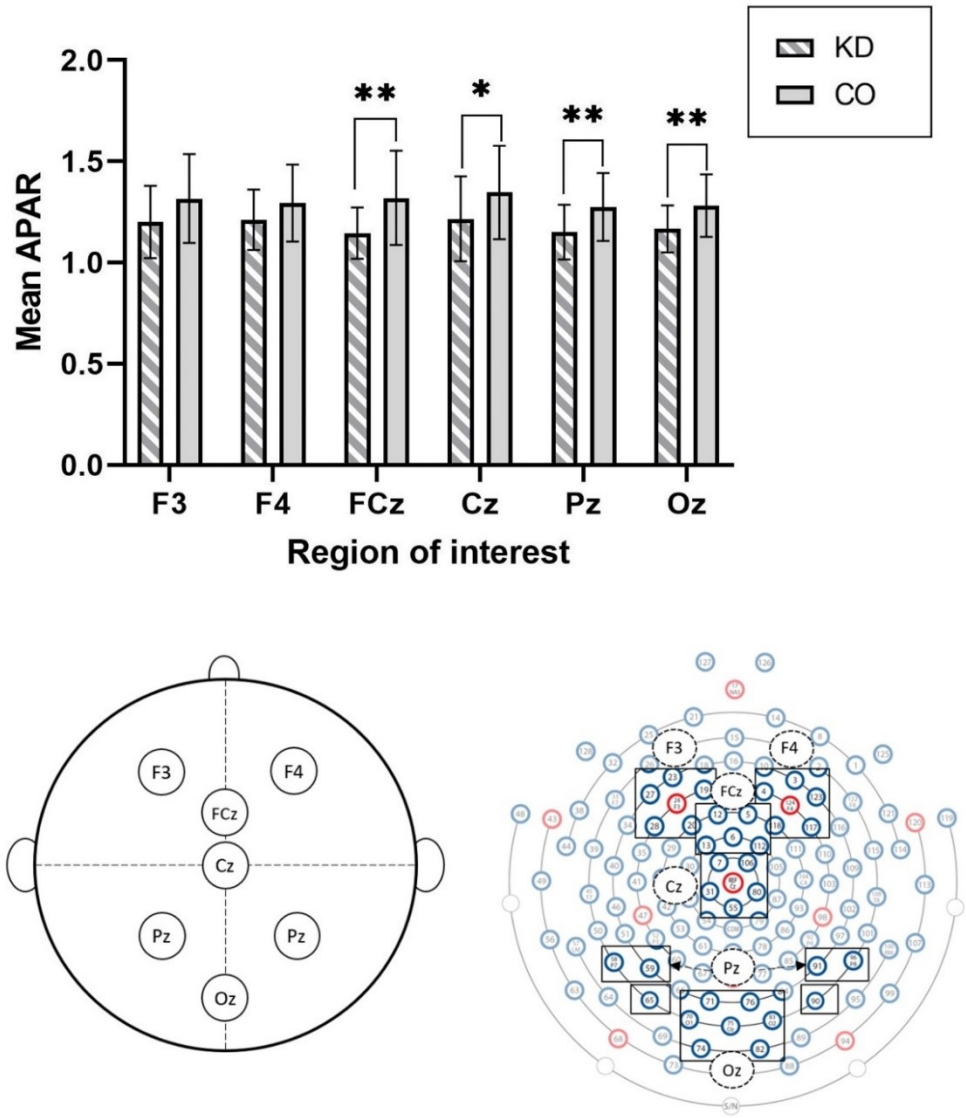

Figure 2. Group comparisons of the alpha peak amplitude ratio.

(**Top**) Mean alpha peak amplitude ratio (APAR) for the Kawasaki disease group (KD – dashed bars) and control group (CO – plain) in the six regions of interest (left frontal (F3), right frontal (F4), frontocentral (FCz), central (Cz), parietal (Pz), and occipital (Oz)). Errors bars are standard deviations. The APAR is significantly lower in KD in FCz, Cz, Pz, and Oz regions (Mann-Whitney U test. *$p < .05$ **$p < .01$). (**Bottom**) Schematic representation of the 6 regions of interest in a 10-20 system of electrode placement (adapted from Electrical Geodesics System Inc.).

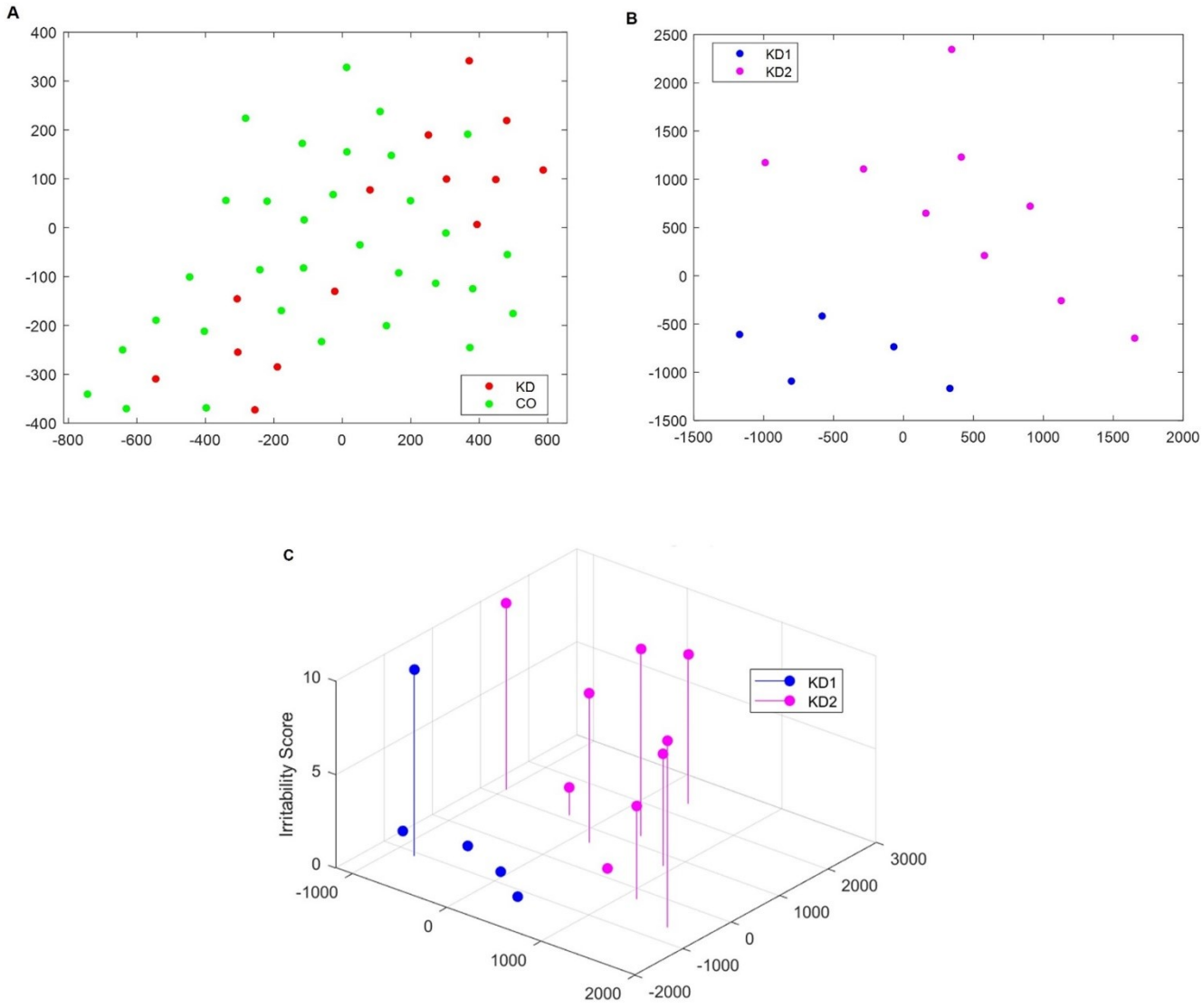

Figure 3. Projection of the high-dimensional alpha PSD curve on a two and three-dimension space (each axis is a vector for visualization).

(**A**) The two-dimensional projection of the 24-dimensional alpha curve profile metrics for KD and CO subjects shows poor separation between groups, while (**B**) KD patient subgroup clustering shows two well separated embeddings as shown in (**C**) where a KD2 subgroup had a higher number of patients with acute irritability as opposed to a KD1 subgroup.